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The role of myelin plasticity in specific CNS functions – learning and memory, reward system

Význam plasticity myelinu pro specifické funkce CNS – učení a paměť, systém odměny

Bachelor's thesis

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Abstract

Neuroplasticity is a fundamental characteristic of the brain that allows it to adapt to changes in the environment, learn new skills or recover from injuries. Although the majority of scientific literature on neuroplasticity has focused on neurons and synaptic changes, recent research suggests another important mechanism that is based on myelin plasticity. The goal of this bachelor thesis is to present a literature review on current research trends in the topic of myelin plasticity. The focus revolves around the function of myelin, the lipid membrane that provides insulation and support to axons, and the concept of myelination as an adaptive process. The relationship between activity-dependent myelination, its triggers, and the effect on specific brain circuits function and dysfunction are thoroughly discussed. Research in myelin plasticity has led to a change in the paradigm of brain plasticity, as there is now clear evidence that the latter cannot be fully understood without taking the former into account.

Keywords: oligodendrocytes, myelination, differentiation, neuronal activity, neuronal circuits plasticity

Abstrakt

Neuroplasticita je základní vlastností mozku, která umožňuje přizpůsobení se změnám prostředí, naučit se novým dovednostem nebo se regenerovat po poranění. Ačkoliv se většina odborné literatury o neuroplasticitě primárně zaměřovala na neurony a změny v synaptických strukturách, současný výzkum naznačuje další významný mechanismus, který je založen na plasticitě myelinu. Cílem této bakalářské práce je uvést přehled literatury o současných trendech výzkumu v oblasti plasticity myelinu. Důraz je kladen na funkci myelinu, lipidové membrány, která poskytuje izolaci a oporu axonům, a na koncept myelinizace jako adaptivního procesu. Obsáhle je diskutován vztah mezi myelinizací závislé na aktivitě neuronů, jejími spouštěči a jejím vlivem na funkci a dysfunkci konkrétních neuronálních okruhů. Výzkum plasticity myelinu vede ke zvratu v paradigmatu neuroplasticity, neboť nyní existují jasné důkazy, že neuroplasticita není plně objasnitelná, aniž bychom vzali v potaz plasticitu myelinu.

Klíčová slova: oligodendrocyty, myelinizace, diferenciacce, neuronální aktivita, plasticita neuronálních okruhů

List of abbreviations

ADM	activity-dependent myelination
BCAS1	brain enriched associated protein 1
BrdU	bromodeoxyuridine
CFC	contextual fear conditioning
Chrm1	muscarinic acetylcholine receptor 1
CNPase	2', 3'-cyclic-nucleotide 3'-phosphodiesterase
CNS	central nervous system
CPP	conditional place preference
DTI	diffusion tensor imaging
EdU	5-ethynyl-2'-deoxyuridine
FA	fractional anisotropy
GalC	galactocerebroside
KO	knockout
MAG	myelin-associated glycoprotein
MBP	myelin basic protein
MOG	myelin oligodendrocyte glycoprotein
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
Myrf	myelin regulatory factor
NAc	nucleus accumbens
NG2	neuron-glia antigen 2
OLCs	oligodendrocyte lineage cells
OPCs	oligodendrocyte precursor cells
PDGF	platelet-derived growth factor
PDGFRα	platelet-derived growth factor receptor alpha
PLP	proteolipid protein
SCoRe	spectral confocal reflectance
TTX	tetrodotoxin
VTA	ventral tegmental area
WT	wild type
α-ScTX	α -scorpion toxin

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Introduction

The nervous system maintains an especially high level of functional plasticity throughout the entire life enabling adequate responses and adaptation to ever-changing external stimuli, though this plasticity diminishes with aging (Burke and Barnes 2006). Traditionally, nervous system plasticity has been attributed to changes in synaptic plasticity including the formation of new synapses and stronger signalling in already formed ones. However, new research has brought insights into novel unexpected form of nervous tissue plasticity mediated by myelin (McKenzie et al. 2014; Liu et al. 2012; S. Pan et al. 2020)

Myelin is a lipid membrane that compactly wraps around axons, allowing for faster signal transmission along them. It plays an essential role in signal arrival synchronisation, where time differences of the order of milliseconds are relevant. Historically, myelin has been considered as a static structure that is set in early development. However, recent research brought evidence that in the central nervous system (CNS), myelination is a protracted and plastic process ongoing throughout adulthood (Hill, Li, and Grutzendler 2018; Hughes et al. 2018).

Myelin plasticity or adaptive myelination are thus new terms describing changes in myelination occurring in the nervous system, which can occur both as a response to changes in neuronal activity and to nervous tissue damage. Within this context, the term activity-dependent myelination (ADM) refers to the responses of oligodendrocyte lineage cells (OLCs) to specific neuronal activity or to neuronal activity in specific neuronal circuits. This type of plasticity has only recently begun to be recognized as a new mechanism of nervous system plasticity (Monje 2018).

Plasticity in the CNS is a fundamental mechanism underlying learning, memory, and reward processing. Since ADM changes can contribute to the adaptive capacity of neuronal circuits, they may facilitate those processes.

The aim of this work is to put together a literature review of recent research showing the response of OLCs to neuronal activity as well as the reciprocal impact of myelin plasticity on the performance of involved circuits and ultimately on brain function. Hopefully, it will provide valuable insight into the emerging field of myelin plasticity and its profound implications on specific cognitive functions, particularly learning and memory, as well as the intricate workings of the reward system.

1. Oligodendrocytes and their development

An oligodendrocyte is a type of glial cell found in the CNS, that forms myelin membranes compactly wrapping around axons. Oligodendrocytes arise from oligodendrocyte precursor cells (OPCs) that have migrated out from the germinal zones in medial ganglionic eminence and become evenly distributed in the CNS during embryonic development (Pringle and Richardson 1993; Kessaris et al. 2006). OPCs maintain their distribution in the CNS throughout life and continue to support *de novo* formation of oligodendrocytes, which provide lifelong myelination of axons (Hughes et al. 2018; Hill, Li, and Grutzendler 2018).

Oligodendrocyte development throughout the life span consists of OPC differentiation into pre-myelinating (immature) oligodendrocytes and then into myelinating oligodendrocytes (Young et al. 2013; Hughes et al. 2013; Pfeiffer, Warrington, and Bansal 1993). Different stages of the oligodendrocyte lineage express different combinations of antigens, morphologies, and membrane properties (Pfeiffer, Warrington, and Bansal 1993; Spitzer et al. 2019) (**Figure 1**).

OLCs can be identified by the expression of transcription factors SOX10 and Olig2. OPCs are also positive for neuron-glial antigen 2 (NG2), platelet-derived growth factor receptor alpha (PDGFR α) and the transcription factor Nkx2.2. (Nishiyama et al. 1996). On the other hand, immature oligodendrocytes start to express the enzyme 2', 3'-cyclic-nucleotide 3'-phosphodiesterase (CNPase), the brain enriched associated protein 1 (BCAS1) (Fard et al. 2017), the O4, and the galactocerebroside (GalC) lipids. Finally, mature oligodendrocytes develop with the expression of myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), myelin-associated glycoprotein (MAG), CNPase, and proteolipid protein (PLP) (Pfeiffer, Warrington, and Bansal 1993).

OPCs differentiate into immature oligodendrocytes but many of them do not engage in the myelination of axons and eventually undergo cell death (**Figure 1**). This is likely due to an overproduction of newly-formed oligodendrocytes in response to neuronal signals (Barres et al. 1992).

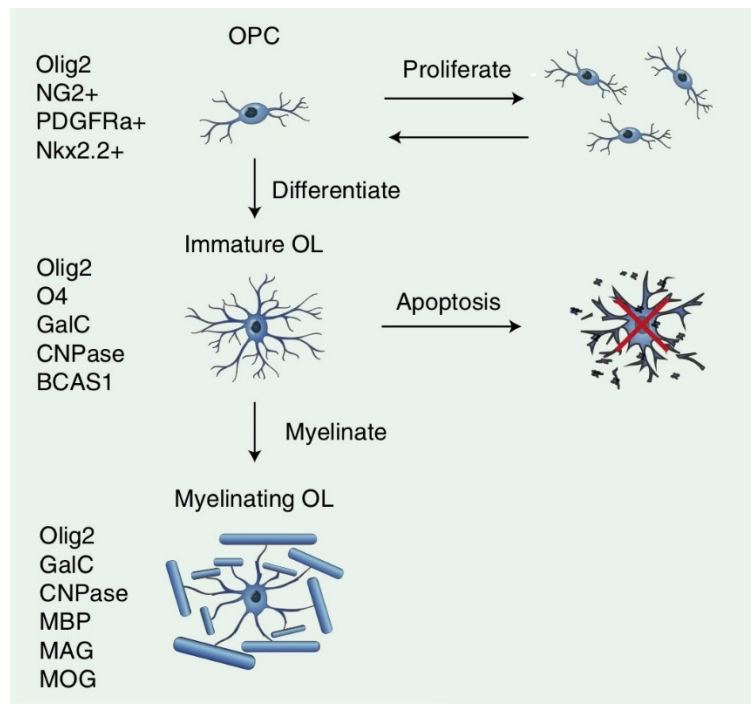


Figure 1: The development of the oligodendrocyte lineage adapted from (de Faria et al. 2021)

2. Myelin

2.1. Myelin structure

Myelin is formed by two types of cells: the Schwann cells and the oligodendrocytes. The former create myelin and insulate axons in the peripheral nervous system by coating a single axon whereas the latter serve a similar function in the CNS by extending processes and enveloping several axons at a time. These processes create multiple layers of overlapping membranes around axons (Snaidero et al. 2014) that form the myelin sheath. The composition of the sheath is roughly made of 20-30% protein and 70-80% lipids (Boggs and Moscarello 1978). In the middle layers, the cell membranes join together with the help of MBP (Boggs 2006), creating compact myelin. Apart from MBP, another main protein present in the compact myelin is the hydrophobic PLP (Jahn et al. 2020).

Other myelin-related proteins that can be found in the myelin sheath are the following (Jahn et al. 2020):

- MOG, localised on the outside surface of myelin sheaths and oligodendrocytes, which can be a target of autoantibodies and therefore, can be used for the identification of myelin (Mayer and Meinel 2012).
- MAG, specifically localised in the periaxonal membranes of oligodendrocytes. It plays a role in interactions between the oligodendrocyte and axon (Quarles 2007).
- CNPase, widely used as an oligodendrocyte marker and associated with the cytoplasmic side of plasma membranes.

2.2. Myelin function in neuronal circuits

The main function of the myelin sheath is to increase the conduction velocity of electrical impulses passing along axons (Sanders and Whitteridge 1946). Far from being a continuous medium, the myelin coverage contains gaps known as the nodes of Ranvier. These nodes are essential for the rapid and efficient transmission of action potentials. They contain a large concentration of voltage-gated ion channels, which allow for the creation of the action potential. The role of the myelin sheath is to provide a decrease in capacitance and the necessary insulation to prevent electrical leakage (Bakiri et al. 2011). This in turn permits the action potential to rapidly spread from one node to another (i.e. saltatory conduction), bypassing the myelinated part of the axon and significantly speeding up the electrical impulse transmission (Huxley and Stampfli 1949).

In the nervous system, the processing of neural information largely depends on the precise timing of signals, from the accurate arrival of action potentials at the cellular level to coordinated motion at the whole-body level. Through changes in myelin sheath length and thickness, the timing of neurotransmission can be modulated (Wu et al. 2012), defining one important function of myelin-forming cells.

Another crucial function of oligodendrocytes is that they provide metabolic support to the myelinated axons (Fünfschilling et al. 2012; Lee et al. 2012). They supply products of their glycolysis (lactate or pyruvate) to axons, supporting in this fashion their energy demands and functional integrity. In experiments on mice where one of the component proteins of the myelin sheath was deleted and, importantly, this absence had little impact on the myelination or the myelin sheath integrity, the mice showed axon loss (Klugmann et al. 1997; Edgar et al. 2009; Lappe-Siefke et al. 2003). This suggests that oligodendroglia support axon survival through a myelin-independent mechanism and it is likely that the induced changes in the myelin sheath structure contribute to these results.

Furthermore, oligodendrocytes play a significant role in spatial buffering of potassium released during axonal activity (Menichella et al. 2006). Spatial buffering is the redistribution of ions in the brain's extracellular space helping to regulate the local microenvironment. High concentrations of potassium could interfere with the normal resting membrane potential of neurons and impair their ability to generate and propagate action potentials effectively, which could lead to disrupted neuronal function.

3. Static myelin versus activity-dependent myelination

When considering the concept of brain plasticity, the initial thought that comes to one's mind is often that it is very limited or nearly non-existent. This follows from the common belief that neurons only proliferate during neurodevelopment, whereas throughout life we are solely experiencing neuronal loss. However, a deeper understanding reveals that neuronal changes carry on over the course of a

lifetime, primarily via the formation of new synapses and dendritic structures (Holtmaat and Svoboda 2009). Therefore, the focus shifts towards viewing brain plasticity mainly as synaptic plasticity. While it is true that neurons undergo adaptation via synaptic plasticity, it is not the only factor at play in the spectrum of factors influencing neural adaptivity.

Traditionally, the myelin sheath has been seen as a static structure of the brain, serving to accelerate axonal conduction and provide metabolic support to axons (Fünfschilling et al. 2012; Lee et al. 2012). However, the pioneering study by Barres and Raff in 1993 showed that neuronal activity can impact OPC proliferation in the adult optic nerve (Barres and Raff 1993). This discovery challenged the conventional view and suggested that myelin and the process of myelination can change in response to external stimuli. In other words, the process of myelination is able to adapt to environmental changes. This new finding introduces a new form of brain plasticity, the ADM.

3.1. Controversies in evidence for activity-dependent nature of myelination

ADM refers to the process in which myelin formation around axons is influenced by neuronal activity, leading to changes in the myelin structure and controlling to what extent certain areas of the brain will be myelinated. Conversely, several studies have observed that oligodendrocytes have a kind of default myelination that happens without axonal firing. For instance, Bechler et al. (2015) conducted experiments on an artificial culture system lacking neurons, substituting them with microfibers (Bechler, Byrne, and Ffrench-Constant 2015). In this experiment, OPCs from two different regions of the brain, the spinal cord and cortex, were cultured on these microfibers. Observations revealed that most OPCs differentiated into oligodendrocytes that, surprisingly, formed multi-layered compacted membranes around the microfibers, resembling physiological conditions in the CNS. The established myelin sheath was positive for typical markers such as MBP and MOG.

Furthermore, another interesting finding from this study came to light: OPCs from different brain regions generated oligodendrocytes with varying sheath lengths, even though they were cultured under the same conditions (Bechler, Byrne, and Ffrench-Constant 2015). This suggests that myelin sheath length is an intrinsic property of oligodendrocytes and it changes depending on their location within the CNS. Specifically, spinal cord oligodendrocytes exhibited significantly longer ensheathment compared to cortical oligodendrocytes, which is consistent with the physiological conditions. In the CNS, oligodendrocytes generally wrap with longer sheaths those axons with larger diameters and axon diameters are larger in the spinal cord (Hildebrand et al. 1993).

Building upon this, the authors continued with the experiment to explore whether oligodendrocytes respond to the diameter of microfibers. OPCs were cultured on microfibers with varying diameters, resulting in oligodendrocytes forming longer and shorter sheaths on microfibers with larger and

smaller diameters, respectively. This is an indication that oligodendrocytes adjust sheath lengths according to this physical property of axons.

In summary, Bechler et al. (2015) demonstrated that OPCs and their descendent oligodendrocytes have some kind of intrinsic, default settings and, that the process of myelination occurs even without neurons and their electrical activity.

Although this sounds contradictory to the idea of ADM, we can see in many studies compelling reasons to believe that myelination is neuronal activity dependent or at least in some contexts (Barres and Raff 1993; Demerens et al. 1996; Gibson et al. 2014; Mitew et al. 2018). An explanation of these contradictions was proposed already in 1896 by Hans Held by suggesting that two modes of myelination occur (Ambronn 1896 in de Faria et al. 2021). The first is activity-independent myelination, which occurs consistently in the same manner. The second mode is ADM, occurring in response to external stimuli provided by active neurons.

Only recently, further evidence has been given by *in vitro* experiments conducted by Lundgaard et al. (2013). The mechanisms governing the switch between these modes are not fully understood, but there is a theory suggesting that this occurs at the level of OPCs. They switch to an activity-dependent state based on the presence of surrounding growth factors together with neuronal activity (Lundgaard et al. 2013). Subsequently, these OPCs then start to express NMDA receptors that make them more susceptible to detect and respond to neuronal activity of nearby axons by differentiation.

4. Forms of activity-dependent myelination

There are various forms in which OLCs respond to the activity of neurons in the adult CNS. On one hand, it can alternate the proliferation and differentiation of OPCs, which then results in the addition of new myelin internodes. On the other hand, alterations occur at the level of mature oligodendrocytes, which can elongate, retract, or adjust the thickness of existing myelin sheaths, or even create new internodes. Both mechanisms are explored in more detail below and represented in **Figure 2**.

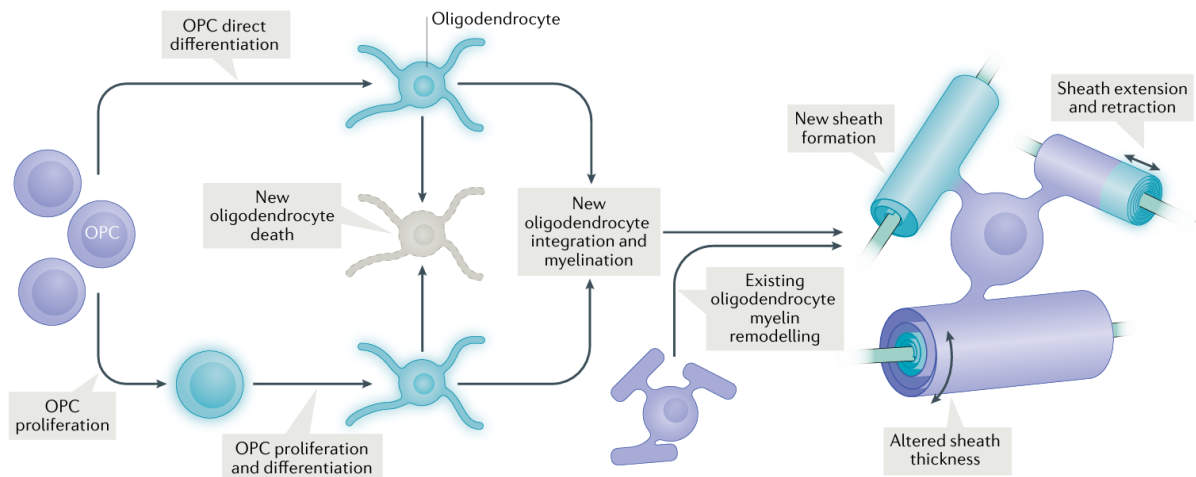


Figure 2: Multiple forms of plasticity within the oligodendrocyte lineage adapted from ((Xin and Chan 2020)

4.1. Activity-dependent proliferation of OPCs

Various studies have elucidated the addition of new myelin internodes resulting from OPC proliferation within the adult brain, employing diverse methodologies *in vivo*. For instance, Gibson et al. (2014) observed changes in OPC proliferation in the premotor cortex following optogenetic stimulation, while Mitew et al. (2018) examined chemogenetic stimulation effects in the somatosensory cortex also resulting in changes in OPC proliferation (Gibson et al. 2014; Mitew et al. 2018). In addition, Hughes et al. (2018) conducted experiments using longitudinal *in vivo* two-photon imaging to demonstrate the lifelong generation of oligodendrocytes and the continuous addition of new internodes in response to sensory stimulation in the somatosensory cortex (Hughes et al. 2018). Particularly in middle-aged mice exposed to enriched sensory environments, such as cages fitted with hanging strings of beads. Assuredly, mice whose whiskers were trimmed did not exhibit the same increase in new myelin formation (Hughes et al. 2018).

Furthermore, a study employing a combination of imaging techniques also demonstrated significant alterations in myelination throughout life (Hill, Li, and Grutzendler 2018). To confirm that observed changes in myelin density were indeed due to the generation of new oligodendrocytes rather than to the generation of new processes by existing oligodendrocytes, researchers employed two imaging techniques. Firstly, label-free spectral confocal reflectance (SCoRe) microscopy by which changes in myelin intensity and segment length can be measured. This allows the visualisation of myelin without fluorescent labels, ensuring that the samples remain in their natural state and minimizing experimental errors. Secondly, fluorescence imaging was utilized to visualize the density of oligodendrocyte cell bodies *in vivo*, providing complementary insights into the changes in myelination.

The proliferation of OPCs might be directly followed by differentiation of one of the daughter cells or possibly even both of the daughter cells, or proliferation could be a secondary cause of OPC differentiation with the objective of restoring the OPC population (Hill et al. 2014) (**Figure 2**).

4.2. Activity-dependent differentiation of OPCs

Rather than proliferating, some OPCs can, instead of proliferation, respond to neuronal activity by directly differentiating into oligodendrocytes (**Figure 2**). Those are the OPCs that have switched into the activity-dependent state as described above. They stand out from the rest due to their higher expression of NMDA receptors. Combined with the presence of growth factors, this enhances their sensitivity to neuronal activity or signals from active neurons (Lundgaard et al. 2013). It seems that in this state, OPCs are “primed” to directly differentiate after acquiring appropriate stimuli (Kamen et al. 2022). This is indeed corroborated by the work of Bacmeister et al. (2020). They utilized *in vivo* imaging techniques to observe the behaviour of OPCs and oligodendrocytes during the process of motor learning, particularly in a task involving forelimb-reaching. Within the four-week duration of imaging, a significant finding emerged: the OPCs present in the motor cortex underwent a differentiation process without proliferating first (Bacmeister et al. 2020).

4.3. Activity-dependent changes in mature oligodendrocytes

Activity-dependent myelin plasticity can also be observed via the adjustment of myelin sheaths at the level of mature oligodendrocytes (**Figure 2**). These dynamic alterations also play an important role in regulating neuronal signalling efficiency and integrity within the nervous system.

There is evidence that the thickness of myelin sheaths might not be static and thus is not fully determined by axon diameter on its own. Differences in neuronal activity might be another reason why myelin thickness changes. Increased thickness of myelin sheaths has been observed as a result of (i) optogenetic stimulation in the premotor cortex (Gibson et al. 2014) and (ii) chemogenetic stimulation of the somatosensory cortex (Mitew et al. 2018) in the mouse adult brain.

On the other hand, it has been shown that myelin sheaths can get thinner around those axons with less activity. For instance, in the auditory tract, adult mice that were ear-plugged exhibited significantly thinner myelin than aged-matched controls (Sinclair et al. 2017).

In addition to changes in thickness, the myelin sheath can also undergo modifications such as retraction or extension. Such changes were observed in a small fraction of myelin sheaths during longitudinal *in vivo* imaging experiments (Hughes et al. 2018; Hill, Li, and Grutzendler 2018).

Furthermore, Krasnow et al. (2018) focused on studying the impact of neuronal activity on developing oligodendrocytes in zebrafish *in vivo*. They found that the changes in neuronal activity influenced calcium transients in developing oligodendrocytes and that the frequency and duration of these transients had an impact on the elongation or retraction of myelin sheaths (Krasnow et al. 2018; Baraban, Koudelka, and Lyons 2018)

The formation of new sheaths by preexisting oligodendrocytes was observed in the context of motor learning (Bacmeister et al. 2020). Conversely, an experiment in zebrafish focused on this topic revealed that oligodendrocytes only produce new myelin sheaths during a brief period after they differentiate from OPCs and generate their initial myelin sheaths (Czopka, French-Constant, and Lyons 2013).

5. Primary observations of activity-dependent myelination

Pilot studies conducted in physiological conditions show a delay in the myelination process in the optic nerve in animals raised in darkness (Gyllenstein and Malmfors 1963). Additionally, they suggest a significant reduction in myelination levels in the naturally blind cape mole rat. In contrast, premature eye-opening seems to quicken the myelination process in the optic nerve (Tauber, Waehnel, and Neuhoff 1980).

A groundbreaking study by Barres et al. (1993) using tetrodotoxin (TTX) in the rat optic nerve showed that the proliferation of OPCs could be dependent on axonal electrical activity (Barres and Raff 1993). TTX blocks voltage-gated sodium channels and thereby inhibits the electrical activity of neurons. The injection of TTX into the eye has shown a significant decrease in OPC proliferation which was quantified using bromodeoxyuridine (BrdU), specifically labelling proliferating cells. Afterwards, these proliferated cells were identified by *in vitro* culturing as OPCs using the A2B5 antibody. Additionally, the study suggested that electrically active axons may stimulate neighbouring glial cells to produce or release platelet-derived growth factor (PDGF), which in turn stimulates OPC proliferation. However, the exact mechanisms remain to be fully elucidated.

The influence of axonal electrical activity on myelinogenesis was furthermore investigated in experiments conducted by Demerens et al. (1996). In *in vitro* experiments, the embryonic mouse brain was treated with TTX or α -scorpion toxin (α -ScTX). When cultures at 8 days *in vitro* were treated with TTX for 2, 4, or 6 days, the number of myelinated fibres at 18-21 days *in vitro* was decreased by 83%, 87%, and 98%, respectively.

If blockade of the neuronal voltage-gated Na^+ channels inhibits myelination, stimulation of neuronal activity by opening the channels should increase myelination. For this purpose, α -ScTX was utilized. This toxin increases neuronal activity by slowing inactivation of voltage-gated sodium channels. In cultures treated with the number of myelinated segments observed 10 days later increased by a factor

of 2.4, compared with control cultures, without a significant effect on the number of MBP positive oligodendrocytes. The *in vitro* effect of TTX and the inverse effect of α -ScTX on myelination is linking the voltage-gated Na⁺ channels and consequently electrical activity to myelination. In *in vivo* experiments, the Mouse Optic Nerve was treated with TTX. Animals in the postnatal day 4 (P4) and P5 showed, 2 days after TTX treatment, a reduced number of myelinating oligodendrocytes by 75 % in comparison to control animals, while the amount of MBP positive oligodendrocytes showed no difference. Demerens et al. (1996) results indicate that within the CNS, the initiation of myelination by oligodendrocytes is triggered by axonal electrical activity.

Direct evidence that neuronal activity regulates changes in oligodendrocytes within an active circuit was demonstrated on awake, behaving mice using *in vivo* optogenetic techniques (Gibson et al. 2014). Optogenetic technology allows to control how neurons fire inside living organisms with very precise timing, down to milliseconds. It is carried out by shining light from a distance of a specific wavelength onto the target cells expressing channelrhodopsin. This method avoids the need for invasive electrodes, which can cause damage to the surrounding tissue. As a result of optogenetic stimulation in the projection neurons in the premotor cortex, robust proliferation of OPCs within the underlying white matter was observed. After 4 weeks, a greater number of newly differentiated oligodendrocytes were observed using 5-ethynyl-2'-deoxyuridine (EdU), a thymidine analogue which incorporates into the DNA during proliferation. Likewise, augmented thickness of myelin sheath in the stimulated premotor cortex was observed. Furthermore, this study represented a type of behaviorally relevant neural plasticity by testing elevated swing speed of the correlate forelimb utilized during the above-mentioned optogenetic stimulation.

Blocking the process of OPC differentiation with drugs prevented the activity-induced formation of oligodendrocytes and changes in myelin, along with the resulting behavioural alterations.

Another study used chemogenetic stimulation of somatosensory axons in the mouse brain to confirm that myelination enhancement is dependent on neuronal activity in both juvenile and adult mice, although in adult mice to a lower extent. It was revealed that the process of selecting axons for myelination is strongly influenced by the relative activity of individual axons within a population. Activation of particular axons results in the increased proliferation and specialization of OPCs within the surrounding white matter. Axons that are stimulated show a higher likelihood of being coated with myelin compared to nearby non-stimulated axons, along with the presence of thicker myelin sheaths (Mitew et al. 2018).

6. Activity-dependent myelination in neuronal circuits

In the above sections, the process of myelination and the two possible modes in which it occurs in the brain have been described. The first mode involves the innate program of myelin development that proceeds independently of neuronal activity. As the second mode, the recent idea of myelin changing accordingly to neuronal activity was introduced and the various forms in which it happens outlined. In the following section, the focus will be on presenting evidence regarding the existence of ADM across diverse neuronal circuits. Evidence will be explored on whether ADM has an impact on the performance of these circuits and the consequences of losing the ability to myelinate axons in response to neuronal activity.

The most intensively studied paradigm in myelin plasticity research is motor learning.

6.1. Motor learning in animal models

Motor learning and its relationship with myelin plasticity was examined in rats on skilled reaching tasks (Keiner et al. 2017) as well as in mice on “complex wheel” running (McKenzie et al. 2014; Xiao et al. 2016) (Figure 3) and pulling-a-lever tasks (Kato et al. 2020).

Keiner et al. (2017) investigated motor learning in adult rats that were trained on reaching task. Skilled animals in this task exhibited an increase in proliferating OPCs and also an increase in oligodendrocytes positive for CNPase indicating that these oligodendrocytes are involved in the formation and maintenance of new myelin (Keiner et al. 2017).


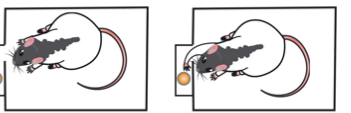
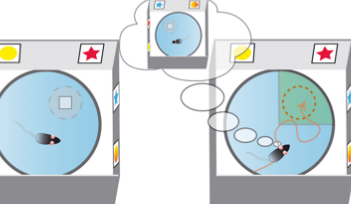
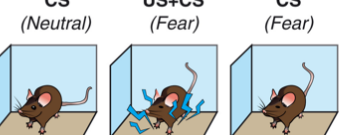
Complex wheel		<ul style="list-style-type: none"> • Motor skill learning task (motor system) • Walk on a wheel with rungs irregularly spaced • Change locomotor pattern between forelimbs and hindlimbs • Measure running speed
Single-pellet reaching task		<ul style="list-style-type: none"> • Motor skill learning task (motor system) • Retrieve a difficult to access food pellet using a single forelimb • Refinement of complex motor programmes • Measure number of successful pellet retrievals
Morris water maze		<ul style="list-style-type: none"> • Spatial memory task (hippocampus) • Reach a platform hidden underneath the water in a large maze • Build a spatial map to “triangulate” and learn the location of the platform using external cues in the environment • Measure time spent in quadrant where the platform was in a probe test
Contextual fear paradigm	 <p>CS (Neutral) US+CS (Fear) CS (Fear)</p>	<ul style="list-style-type: none"> • Context-dependent emotional memory (hippocampus) • Predict the occurrence of aversive stimulus • Build a pavlovian association between the aversive stimulus and the context in which it is presented • Measure time expressing the conditioned fear response in the context in the absence of the aversive stimulus

Figure 3: Behavioural model experiments. An introduction to the four behavioural paradigms in which oligodendrogenesis and the role of de novo myelination have been investigated. Adapted from (Bonetto, Belin, and Káradóttir 2021)

In the “complex wheel” task, mice were to run on a wheel with irregularly interspaced rungs (McKenzie et al. 2014). Learning this new motor skill accelerated the production of newly formed oligodendrocytes which was tested by using genetically modified mice lacking myelin regulatory factor (Myrf). Myrf is a transcription factor that is specifically present in mature, myelinating oligodendrocytes and promotes the expression of many genes important in the production of myelin. Deletion of Myrf in OPCs during adulthood prevented new myelination by blocking the formation of new oligodendrocytes. It was performed without affecting preexisting oligodendrocytes and without triggering demyelination (McKenzie et al. 2014). Therefore, Myrf knockout (KO) mice were prevented from mastering the complex wheel running skill. McKenzie et al. (2014) have shown that active myelination during adulthood is required for motor skill learning and that the latter increases oligodendrocyte production. A follow-up study (Xiao et al. 2016) showed that oligodendrocyte development is crucial for adult mice motor learning soon after they encounter a complex running wheel. Rapid differentiation of oligodendrocytes shortly (within a few hours) after wheel exposure was observed, followed by subsequent waves of OPC proliferation and differentiation, suggesting a response to the earlier decrease in OPC density. This very early requirement for oligodendrocytes suggests a direct and active role in learning. The secondary wave happened together with running performance improvement, indicating that the later-generated oligodendrocytes also contribute to learning and long-term motor memory.

Kato et al. (2020) investigated motor learning ability in a transgenic mouse model trained to pull and hold a lever for 600ms to obtain a reward. The mice in this model exhibited subtle impairments in myelination, characterized by thinner myelin and abnormal oligodendrocyte processes. These impairments were induced by the introduction of extra copies of the myelin PLP 1 gene. These mice displayed impaired learning and decreased performance in this task compared to wild type (WT) mice. The authors attributed these findings to the impaired synchrony of spike time arrival in the thalamocortical pathway, which plays a significant role in learning. Therefore they concluded that impaired myelin disrupts cortical neuronal activity and results in impaired motor learning.

In summary, motor learning or motor behavioural improvements in rodents require proliferation and differentiation of OPCs and generally optimal progress of ADM in the white matter and motor cortex (McKenzie et al. 2014; Xiao et al. 2016; Kato et al. 2020).

6.2. Motor skills-based white matter plasticity in human imaging studies

Learning a new motor skill alters the structure of the brain’s white matter. In human studies, scientists are trying to look into that using non-invasive brain imaging techniques. The most commonly used approaches rely on magnetic resonance imaging (MRI). MRI is a non-invasive medical imaging

technique which uses magnetic fields and radio waves to create detailed images of the body's internal structures.

To image the white matter tract of the brain, there is a special modality of MRI, the diffusion tensor imaging (DTI), which focuses on measuring the diffusion of water molecules in brain tissues. As the water diffuses through different structures of white matter the technique measures different parameters which then reflect the microstructural organization. In the case of myelination, fractional anisotropy (FA) is often considered the most important parameter (Shemesh 2018; Mädler et al. 2008).

There are various studies observing changes in FA which accompany learning and training skills. Bengtsson et al. (2005) investigated the effect of piano practice on white matter (Bengtsson et al. 2005). Correlating hours of piano practice with FA measurements, they proposed increased myelination as a result of neuronal activity in fibre tracts during training. Furthermore, they proposed a positive correlation between engaging in training during childhood, a period when a larger number of fibre systems have not yet matured, and the likelihood of pursuing a career as a professional pianist.

Scholz et al. (2009) detected a consistent increase of FA in white matter following training of a complex visual-motor skill such as juggling (Scholz et al. 2009). They observed that structural changes did not correlate with the performance level achieved by individuals, but most likely were associated with the time spent in training.

Another study aimed to shed light on the cellular events that underlie the measures obtained in human neuroimaging studies of motor learning (Sampaio-Baptista et al. 2013). To achieve this, researchers combined MRI with immunohistochemistry techniques on rats trained in a novel motor skill. Indeed, they found a positive correlation between learning rate and FA and an increase in MBP expression in the same brain area. However, they did not report any correlation between measures of MBP expression and FA. This might be because of the complexity of DTI diffusion parameters. Particularly, FA is modulated by several white matter characteristics, such as axon diameter, axon packing, and fibre organization (Beaulieu 2002).

It is possible that myelin is but one aspect of the white matter that has undergone plasticity and FA is capturing several white matter features, thus a correlation cannot be established. Or FA reflects primarily diffusion properties of axons and very little the amount of myelin covering the axons.

6.3. Spatial memory

To test the role of ADM in spatial memory and its significance in memory consolidation, researchers trained mice to remember the location of a hidden platform inside a water maze (Steadman et al. 2020; Wang et al. 2020) (**Figure 3**).

In the experiments by Steadman et al. (2020), the adult WT mice spatial learning was examined in contrast to mice with *Myrf* deletion. First, in WT mice, it was found that spatial learning in the water maze induces oligodendrogenesis. New oligodendrocytes were generated both during training and shortly after. These changes primarily took place in cortical and related white matter areas known for their role in the long-term consolidation of spatial information. Second, inducing *Myrf* deletion during or right after training resulted in less time spent in the hidden platform area, suggesting that the blockade of oligodendrogenesis either during or right after training hindered the consolidation of spatial memories. Preventing oligodendrogenesis 25 days after training didn't show any difference between WT and *Myrf* KO mice in locating the hidden platform, which proposes the existence of a specific post-training time window for ADM contributing to memory consolidation.

Further examination demonstrating that myelination contributes to spatial memory applied the inhibition in contrast to stimulation of myelination (Wang et al. 2020). In adult mice, conditional deletion of *Olig2*, an important transcription factor in mechanisms regulating the OPC differentiation (Mei et al. 2013), resulted in a significant decrease in the number of oligodendrocytes and myelin sheaths in the corpus callosum, cortex and hippocampus. In subsequent water maze testing *Olig2* KO mice exhibited lower performance compared to control. In older mice, the enhancement of oligodendroglial differentiation and myelination was tested to assess whether it could improve memory function. The processes of myelination are inhibited to a great extent in the aged CNS by various inhibitory mechanisms (Neumann et al. 2019). The enhancement was achieved through the deletion of muscarinic acetylcholine receptor 1 (*Chrm1*), which was observed to be a negative regulator of oligodendroglial differentiation and myelination (Mei et al. 2016). *Chrm1* KO mice displayed a substantial increase in myelin expression in the corpus callosum, cortex, and hippocampus at 18 months compared to WTs. Furthermore, *Chrm1* KO mice exhibited improved performance in water maze tasks. Another approach was used in order to enhance myelination, the Clemastine fumarate, a first-generation antihistamine with an anti-muscarinic effect (Mei et al. 2014). This treatment in 12-month-old mice not only enhanced myelination but also preserved spatial memory capacity in the water maze test.

These findings underscore that ADM contributes to the consolidation and retrieval of spatial memory by influencing the activity of neuronal circuits associated with it, subsequently impacting the spatial memory behaviour of mice.

6.4. Fear memory – cognitive function

For the investigation of mouse cognitive functions, researchers have focused on examining the mouse fear memory by introducing the contextual fear conditioning (CFC). This is a behavioural experiment where a new environment (context) is linked with an unpleasant stimulus, such as an electric shock

(Figure 3). Such pairing creates an association between the neutral setting and the negative experience, resulting in the animal or subject displaying fear responses when placed back into the same context, even without the presence of the aversive stimulus. The fear response in mice is assessed by the duration of their immobility, commonly referred to as freezing behaviour.

Steadman et al. (2020) conducted an experiment based on the hypothesis that experience-induced oligodendrogenesis in the adult brain is important for memory consolidation. This is because it coordinates neuronal activity across brain regions and, in particular, synchronises rhythmic oscillations (Pajevic, Basser, and Fields 2014). More precisely, the synchronization between spindle oscillations in the prefrontal cortex and ripple oscillations in the hippocampus contributes significantly to the consolidation of memories (Siapas and Wilson, 1998). Learning leads to an increase in ripple-spindle synchronization, and this increased oscillatory coupling appears to play an essential role in memory consolidation (Maingret et al. 2016). The inhibition of oligodendrogenesis, by for instance deletion of *Myrf*, should then impair this ripple-spindle synchronization and therefore impair memory consolidation.

To investigate the above hypothesis, Steadman et al. (2020) utilised a CFC paradigm, as it engages hippocampal-cortical circuits, in *Myrf* KO and control mice (Steadman et al. 2020). Following training, neural activity was recorded, and memory was assessed 28 days later. *Myrf* deletion disrupted the conditioning-induced increase in ripple-spindle coupling observed in control mice. The disruption was confirmed using two coupling metrics. Importantly, *Myrf* KO mice froze for significantly less time during remote, not recent, memory tests, indicating impaired memory consolidation. These findings suggest that oligodendrogenesis is vital for enhancing coordinated neural activity between the hippocampus and prefrontal cortex, thereby affecting contextual and spatial memory consolidation.

Another study provides evidence of ADM influencing fear memory and neuronal circuit performance (S. Pan et al. 2020) by demonstrating that fear learning induces OPCs to proliferate and differentiate into myelinating oligodendrocytes in the medial prefrontal cortex (mPFC). In this experiment, WT mice were subjected to CFC and after 24 hours their fear memory was tested. Mice froze in a conditioning context, suggesting successful fear learning. Histological tests were performed using EdU and Olig2 markers to point out newly proliferated OLCs. They confirmed increased proliferation of OPCs in the mPFC compared to controls that were not subjected to CFC.

Subsequently, two tests of freezing responses 24 hours and 30 days were made on WT mice after subjecting them to CFC. In the mPFC, the number of cells marked by EdU and ASPA increased. ASPA is a marker for differentiated oligodendrocytes. Still, there was no change in the total number of cells marked by both EdU and Olig2, indicating that a subpopulation of OPCs must have differentiated into oligodendrocytes.

New myelin formation was then inhibited by deleting *Myrf*, mice showed high freezing levels in the recent fear memory recall just as the control. However, in the remote recall, *Myrf* KO mice started showing a decrease in freezing levels.

The last experiment examined what would happen to fear memory recall if myelination was enhanced by giving the animals the pro-myelinating drug clemastine fumarate (Mei et al. 2014; Green et al. 2017). Animals were given clemastine three days before they experienced fear conditioning, and this continued until 21 days after the conditioning. When they were exposed to the context again 30 days later, the ones treated with clemastine froze more compared to those given just the vehicle. Notably, clemastine did not affect freezing in *Myrf* KO animals, suggesting it works by influencing OPC differentiation. It appears that maintaining fear memory relies on new oligodendrogenesis, which can be enhanced by clemastine.

Overall, the study implies that the ability to myelinate axons in response to neuronal activity plays a crucial role in the consolidation and retrieval of fear memories and influences the activity of neuronal circuits associated with fear responses. Loss of the ability to form new myelin in response to neural activity may lead to deficiencies in fear memory recall and fear memory behaviour.

6.5. Sensory experience

The relationship between ADM and sensory experience was observed in the visual and somatosensory cortex of adult rats (Murphy et al. 2020). Examining the expression of MBP provided insights into the impact of sensory experience on myelination. While sensory enrichment caused an increase in MBP expression in the somatosensory cortex, monocular deprivation led to hemisphere-specific changes in MBP expression, increasing it in the non-deprived hemisphere and decreasing it in the deprived hemisphere of the visual cortex. Another study examined the effect of housing rats in an enriched environment on the generation of oligodendrocytes in the adult sensorimotor cortex (Keiner et al. 2017). A significant increase of newly differentiated oligodendrocytes in the sensorimotor cortex was observed on day 42 of an enriched environment.

6.6. Social isolation

Liu et al. (2012) observations suggested that myelination acts as a form of adult plasticity (Liu et al. 2012). They state that adult myelin plasticity is modulated by social experiences. To proof this hypothesis, adult mice were deprived of social contact for 8 weeks. The impact was investigated on the prefrontal cortex which is known to be crucial for complex emotional and cognitive behaviour. Indeed, isolated mice showed reduced social interactions. Ultrastructural analysis revealed thinner

myelin in the prefrontal cortex but not in other areas linked to social interactions. Decreased myelin gene transcripts were also observed in the prefrontal cortex of these mice, paralleled by changes in the amount of protein.

Another study also aimed at understanding how social experience affects the prefrontal cortex myelination and function. Male mice were housed at the beginning of weaning (P21) in isolated, regular, or enriched environments (Makinodan et al. 2012). After 4 weeks, isolated mice showed impaired sociability and working memory, with no changes in locomotion, which indicated that the change in social behaviour was specific. Subsequent analysis revealed simpler oligodendrocyte morphology and reduced expression of myelin genes in isolated mice, alongside thinner myelin in the prefrontal cortex. Further isolation tests starting after P35 showed no differences in oligodendrocyte morphology and myelin gene expression compared to normally housed mice by P65. However, mice isolated from P21 to P35 and returned to regular housing until P65 displayed abnormal oligodendrocyte morphology. These changes were confirmed in behavioural tests as well. This suggests that there is a sensitive time window for myelination in mice after which no major changes take place. Makinodan et al. (2012) also proposed the mechanism by saying that thinner myelin resulting from social isolation alters the conduction velocity of myelinated prefrontal cortex axons, leading to abnormal information processing and subsequent deficits in social behaviours and working memory.

Social isolation during a specific age or time window of sensitivity impairs adult myelination in the mouse prefrontal cortex and causes behavioural deficits (Liu et al. 2012; Makinodan et al. 2012).

6.7. Reward system

Myelin plasticity might be an important part of the reward learning process (Yalçın et al. 2022). The reward system is a neuronal pathway involved in motivating behaviour. When we engage in activities that promote survival or pleasure, such as eating, socializing, or engaging in enjoyable activities, the reward system is activated, reinforcing these behaviours and motivating us to repeat them. It is primarily mediated by the release of neurotransmitters such as dopamine and serotonin in key brain regions including the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (Arias-Carrión et al. 2010).

Experiments were conducted to clarify the role of myelin plasticity in the context of the reward system (Yalçın et al. 2022). The reward circuit activity was stimulated either using optogenetics or by morphine administration. Increased oligodendrogenesis compared to controls was observed in both of these stimulations. However, *in vitro* experiments on the effect of dopamine or morphine alone

indicated that dopamine nor morphine does not directly influence OPC proliferation, suggesting indirect mechanisms, which possibly involve neuron-OPC interactions.

Furthermore, the authors conducted a form of Pavlovian conditioning where they induced conditional place preference (CPP) (Cunningham, Gremel, and Groblewski 2006) by administering morphine within a neutral context. Subsequently, that context becomes associated with the rewarding or aversive properties of a stimulus.

Morphine-treated mice preferred to stay in the morphine-conditioned place and exhibited an increase in oligodendrogenesis. In addition to that, the mice exhibited increasing locomotor activity in response to repeated injections. This is a form of behavioural sensitization (Thomas et al. 2001) where repeated exposure to a stimulus, such as a drug, leads to an amplified behavioural response over time. In the context of drug use, behavioural sensitization manifests as an increase in the intensity or frequency of drug-seeking or drug-taking behaviours with repeated exposure.

In the subsequent phase of the experiments, while undergoing morphine conditioning, the generation of new oligodendrocytes was blocked utilizing a conditional *Myrf* KO in OPCs. This oligodendrogenesis inhibition led to a reduction in oligodendroglial response and disrupted morphine-induced CPP behaviour, yet had no impact on locomotor sensitization. These findings indicate that oligodendrogenesis is necessary for morphine-induced reward learning but not for intrinsic reward behaviours.

The study continued by hypothesising that the dopaminergic neuronal activity of the reward system is strengthened and synchronised by myelination, which leads to fine-tuned release of dopamine and ultimately promotes reward learning and memory retrieval. By monitoring real-time dynamics of dopaminergic release and behaviour in control and *Myrf* KO animals, they observed (i) increased dopamine levels in control animals upon entering the conditioning chamber (anticipating reward) (W.-X. Pan et al. 2005) and (ii) significantly blunted dopaminergic response in *Myrf* KO animals, indicating that the *Myrf* KO animals did not learn the association between the chamber and the previous morphine rewards.

In summary, Yalçın et al. (2022) experiments show that oligodendroglial lineage cells respond to dopaminergic neuronal activity, presumably via neuron-OPC interactions. These activity-dependent changes in myelination are critical for the synchronization of dopamine release and therefore for reward learning. Animals with blocked new oligodendrocyte generation lack the learned dopaminergic response. Even if this study indicates the role of ADM in reward circuits it has been published as a preprint and still awaits the proper reviewer process.

7. Activity-dependent myelination in CNS disorders

Apart from its role in learning and memory formation, ADM might have a crucial effect in CNS regeneration. Myelin regeneration accompanies the restoration of neuronal function after pathological conditions where demyelination takes place. This is the case for instance in CNS ischemic injury or demyelinating disorders such as multiple sclerosis (Duncan et al. 2009; Zawadzka et al. 2010)

Gautier et. al. (2015) showed that ADM may be the mechanism through which remyelination *in vivo* happens (Gautier et al. 2015). Specifically, there is evidence that demyelinated axons generate synaptic contact with OPCs and send them signals via synaptic release of glutamate. OPCs recognize these signals through their AMPA receptors and start to differentiate into new myelinating oligodendrocytes, which ultimately contribute to the processes of remyelination. Furthermore, by blocking neuronal activity, glutamate release, or AMPA receptors, they observed that OPCs continue to proliferate but stop differentiating, which results in impaired remyelination. Impaired signalling from demyelinated axons to OPCs then arises as a plausible mechanism contributing to a failure of remyelination in many demyelinating diseases.

Furthermore, Ortiz et. al. (2019) found out by using optogenetic stimulations in adult mice that recurrent but moderate neuronal activity in damaged tissue is needed to promote and enhance remyelination and, therefore to restore the loss of function in harmful environments (Ortiz et al. 2019).

Conclusions

During the last few decades, research on the role that OLCs play in brain plasticity has seen a significant boost. As a result, there is now enough evidence showing that OLCs are capable of responding to the activity of neurons by altering the myelination process.

Numerous experiments have shown this competence of OLCs to have important consequences on brain function and plasticity. ADM turns out to be associated with motor learning and with the ability to form associative memories and recall them (i.e. memory consolidation and memory retrieval) being a part of cognitive functions. By setting up the experiments where the ADM is inhibited, researchers were able to establish the relationship between the above-mentioned brain functions and ADM. Moreover, it is apparent that ADM contributes to the learning of the reward association within the reward system and is essential in remyelination during demyelinating disorders and other brain injuries.

However, the exact mechanism by which OLCs are contributing to learning is still largely unknown. Newly differentiated oligodendrocytes could play a permissive role by repairing myelin damage to ensure the neural circuits are capable of learning. Alternatively, they might have a more direct involvement. For instance, by changing the conduction velocity they could make the individual circuits more efficient, or by transferring energy substrates like lactate and pyruvate into axons they could ensure their energy and functional integrity (Fünfschilling et al. 2012; Lee et al. 2012).

While ADM stands as an important mechanism supporting fundamental brain functions, it is only in conjunction with synaptic plasticity that leads to global neural plasticity, enabling the brain to adapt, learn, remember and recover from injuries. However, the exact contribution that ADM makes to this puzzle remains unknown.

A general limitation of the reviewed literature is perhaps the fact that most of the experiments were carried out using a single model for inhibition of ADM by disrupting oligodendrogenesis using *Myrf* gene deletion. In mice lacking *Myrf*, oligodendrogenesis is disrupted across the entire brain, impacting also the regions that are not involved in the particular type of learning. Therefore, we cannot be sure that adaptive myelination is solely responsible for the behavioural deficits observed. Or simply, the disruption of the physiological workings of *Myrf* in *Myrf* KO mice could potentially influence the results of conducted experiments. *Myrf* acts as a transmembrane protein requiring cleavage to activate myelin-associated genes (Bujalka et al. 2013). Its uncleaved form might have additional functions within OPCs. It would be desirable in the future to see new research work taking into account different models (Howng et al. 2010; Wang et al. 2020) so that the role of ADM can be appropriately tested.

Exciting advancements in neuroscience, particularly in our understanding of oligodendrocyte's role in learning and memory, and the first observation of it in the reward system, mark a promising moment.

While progress has been made, there's still much to explore and many intriguing mysteries lie ahead on the journey of fully understanding the myelin plasticity.

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